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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

**MEMORANDUM**

Date: June 29, 2004

Subject: Interim Human Health Risk Assessment of 1,2,4-Triazole to Support Tolerance Extensions and New Section 18 Soybean Tolerances for Triazole-Derivative Fungicides.

Data Package Number: 304288
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The Health Effects Division is providing this interim human health assessment for aggregate exposure to 1,2,4-triazole to support the extension of existing parent triazole-derivative fungicide tolerances and establishment of time-limited tolerances associated with Section 18 emergency exemptions for the use of triazole-derivative fungicides to control soybean rust. This assessment should be considered to be highly conservative. The exposure and risk estimates presented in this assessment are overestimates of actual likely exposures. This assessment should be considered interim due to the ongoing series of studies being conducted by the U.S. Triazole Task Force (USTTF). Those studies are designed to provide the Agency with more complete toxicological and residue information for free triazole and are expected to be submitted to the Agency in late 2004. Upon completion of review of these data, HED will prepare a more sophisticated assessment based on the revised toxicological and exposure databases.

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Triazole-derivative fung cides may be metabolized to form 1,2,4-triazole (a.k.a. free triazole), which has been identif ed as a residue of concern by the HED. The Agency has requested a number of studies e: amining the hazard and exposure aspects of 1,2,4-triazole. Much of that work was compile ! by the U.S. Triazole Task Force (USTTF) and submitted to the Agency in Novenber 2002 as th *Profile of the Triazole-derivative Fungicide Compounds and their Common Metabolites* (a.k.. . USTTF Omnibus Report; MRID 45575501). Generally, the Agency found the approach use by the USTTF to be reasonable and conservative with respect to their exposure assessment (M. L oherty, D280913, 4/2/04). This interim assessment relies heavily on the data presented in he Omnibus Report.

*Toxicology*. The toxicol gical database for 1,2,4-triazole is incomplete. In November, 2002, an *ad hoc* Peer Review C mmittee met with the OPP Triazole Team to review the available 1,2,4-triazole toxicolo ical and dietary exposure data. The Committee recommended that a NOAEL of 30 mg/kg and n uncertainty factor of 1000 (10x intraspecies, 10x interspecies, 10x database) be used for both a ute and chronic risk assessments (TXR No. 0052011). That NOAEL is from a rat developme ital toxicity study with a LOAEL of 100 mg/kg/day based on decreased body weight and body weight gain in dams and reduced body weights, increased skeletal variations and undescen led testes in fetuses. Since that time, preliminary data available from the USTTF has indicated tl at use of the 30 mg/kg NOAEL may not be sufficiently protective to serve as the basis f r human health risk assessments. Specifically, preliminary summary data presented by the U STTF to EPA indicate that reduced body weight was seen in male rats at all doses evaluated i the reproductive toxicity study currently underway (estimated LOAEL of approximately 15 mg kg/day). Complete results from this study are currently unavailable to EPA, and the mag nitude of the effect at the estimated LOAEL is unknown. Preliminary data also indicate ad verse effects in other studies currently underway, including the rabbit developmental toxicity stu dy, the subchronic toxicity study in mice, and the subchronic/neurotoxicity study i rats. Based on the limited information available at this time, the body weight effects in the re roduction study occur at a lower dose than effects seen in other studies. Thus, the most conserva tive endpoint currently available for use in risk assessment is a LOAEL of 15 mg/kg/day, based on body weight decreases in male rats in the reproductive toxicity study. For the purposes of the current interim risk assessment, this endpoint, with an uncertainty factor of 1000 (as pr viously recommended by the Peer Review Committee) will be used for both acute and chronic d ietary risk, resulting in an RfD of 0.015 mg/kg/day. The uncertainty factor of 1000 addres ses aspects of the toxicology of 1,2,4-triazole related to potential enhanced susceptibility of infants and children; thus, no special FQPA Safety Factor is being used. The resulting popul tion-adjusted dose (PAD) is 0.015 mg/kg/day. When more complete toxicological informati n becomes available, this point of departure, set of uncertainty factors, and RfD/PAD will be re- examined.

*Dietary Exposure*. Includ ed in the USTTF Omnibus Report is an acute dietary exposure assessment that is based on using the highest triazole-derivative fungicide tolerance level combined with worst-case molec ular weight and plant/livestock metabolic conversion factors. Generally, levels of free triazole n plant matrices are low due to the conjugation of 1,2,4-triazole with serine to form triazolylalani ne followed by oxidation to triazolylacetic acid. In livestock,

the primary terminal residues are parent triazole-derivative fungicide and, depending on the nature of the parent compound, free triazole. HED's review of the Omnibus Report found that this approach provides a conservative estimate of all sources for 1,2,4-triazole except the *in-vivo* conversion of parent compounds to free-triazole following dietary exposure. The degree of animal *in-vivo* conversion is dependent on the identity of the parent fungicide. In rats, this conversion ranges from 0 to 77% (Table 1). For purposes of this interim assessment, HED is using the dietary exposure estimates provided by the USTTF and adjusting them based on the highest rate of conversion observed for any of the parent triazole-derivative fungicides to account for this metabolic conversion (i.e., multiplying exposure estimates by 1.77). The assessment includes residue estimates for all food commodities with either existing or pending triazole-derivative fungicide registrations. The resulting acute dietary exposure estimates (Table 2) are extremely conservative and range from 0.0032 mg/kg/day for males 20+ years old to 0.014 mg/kg/day for children 1 to 6 years old. Estimated risks range from 22 to 93% of the PAD. The USTTF did not conduct a chronic dietary exposure assessment. In order to estimate chronic exposures via food, HED has used the 70$^{th}$ percentile of exposures from the acute assessment (Table 3). Typically, HED uses central tendency values when examining chronic dietary exposure. Use of the 70$^{th}$ percentile provides a reasonable estimate of the mean from the exposure distribution due to the log-normal nature of that distribution (pers. comm. D. Miller, OPP/HED, 4/16/04 and J. R. Tomerlin, OPP/RD, 4/17/04). The dietary assessment does not include potential exposure via residues in water (see below). HED emphasizes that the use of both highest-tolerance-level residues and the highest *in-vivo* conversion factor results in dietary risk estimates that far exceed the likely actual risk.

**Table 1. Summary of Maximum Rat *In-vivo* Conversion of Triazole Fungicides to Free Triazole.**

| Triazole-derivative Fungicide | Maximum Observed % *In-vivo* Conversion to 1,2,4-Triazole in Rats |
|---|---|
| Bromuconazole | Not Available |
| Cyproconazole | 38 |
| Difenoconazole | 14 |
| Diniconazole | 15 |
| Fenbuconazole | 2.5 |
| Flusilazole | 67 |
| Hexaconazole | 18 |
| Myclobutanil | 10 |
| Paclobutrazole | 0 |
| Propiconazole | 5 |
| Tebuconazole | 5.4 |
| Tetraconazole | 77 |
| Triadimefon | 22 |
| Triadimenol | 22 |
| Triticonazole | 15 |
| Uniconazole | 15 |

| Table 2. Summary of Acute Dietary Exposure and Risk Estimates for 1,2,4-Triazole | | | |
|---|---|---|---|
| Population Subgroup | Exposure Estimate, mg/kg/day[a] | Corrected Exposure Estimate, mg/kg/day[b] | % PAD[c] |
| U.S. Population | 0.003356 | 0.005940 | 40 |
| All Infants | 0.006504 | 0.011512 | 77 |
| Non-nursing infants (<1 year old) | 0.007173 | 0.012696 | 85 |
| Children 1-6 years old | 0.008006 | 0.014171 | 94 |
| Children 7-12 years old | 0.003543 | 0.006271 | 42 |
| Females 13-50 years old | 0.001882 | 0.003331 | 22 |
| Males 20+ years old | 0.001830 | 0.003239 | 22 |

[a] Exposure estimates are from the *Profile of the Triazole-derivative Fungicide Compounds and their Common Metabolites* (MRID 45575501). These estimates are based on dietary analysis using the Dietary Exposure Evaluation Model (DEEM) version 7.7 using consumption data from the 1994-1998 Continuing Surveys of Food Intake by Individuals (CSFII). Exposure values are at the 95th percentile.
[b] Exposure estimated multiplied by 1.77 to account for the maximum potential *in-vivo* conversion of parent triazole-derivative fungicide to 1,2,4-triazole.
[c] Population-adjusted dose = 0.015 mg/kg/day. % PAD = Corrected Exposure ÷ PAD × 100.

| Table 3. Summary of Chronic Dietary Exposure and Risk Estimates for 1,2,4-Triazole | | | |
|---|---|---|---|
| Population Subgroup | Exposure Estimate, mg/kg/day[a] | Corrected Exposure Estimate, mg/kg/day[b] | % PAD[c] |
| U.S. Population | 0.001115 | 0.001974 | 13 |
| All Infants | 0.002211 | 0.003913 | 26 |
| Non-nursing infants (<1 year old) | 0.002686 | 0.004754 | 32 |
| Children 1-6 years old | 0.004000 | 0.007080 | 47 |
| Children 7-12 years old | 0.001905 | 0.003372 | 22 |
| Females 13-50 years old | 0.000850 | 0.001505 | 10 |
| Males 20+ years old | 0.000894 | 0.001582 | 11 |

[a] Exposure estimates are from the *Profile of the Triazole-derivative Fungicide Compounds and their Common Metabolites* (MRID 45575501). These estimates are based on dietary analysis using the Dietary Exposure Evaluation Model (DEEM) version 7.7 using consumption data from the 1994-1998 Continuing Surveys of Food Intake by Individuals (CSFII). Exposure values are at the 70th percentile.
[b] Exposure estimated multiplied by 1.77 to account for the maximum potential *in-vivo* conversion of parent triazole-derivative fungicide to 1,2,4-triazole.
[c] Population-adjusted dose = 0.015 mg/kg/day. % PAD = Corrected Exposure ÷ PAD × 100.

*Residential Exposure*. Triazole-derivative fungicides are registered for use on turf, resulting in the potential for residues of free triazole in grass and/or soil. Thus dermal and incidental oral exposures to children may occur. It is believed that residues of free triazole occur within the plant matrices and are not available as surface residues. Therefore, direct dermal exposure to 1,2,4-triazole due to contact with plants is not likely to occur. However, dermal exposure to parent fungicide and subsequent *in-vivo* conversion to 1,2,4-triazole may occur. In order to account for this indirect exposure to free triazole, HED is using a conversion factor of

10%, which is the highest rate of *in-vivo* conversion observed in rats for any of the triazole-derivative fungicides with registrations on turf. Incidental oral exposure may occur by direct and indirect routes. To assess direct exposure, HED has used a conversion factor of 17%, which is the highest rate of conversion to free triazole observed in any of the plant metabolism studies. As with indirect dermal exposure, HED has used a conversion factor of 10% in its assessment of indirect oral exposure. The residential exposure values in this assessment are taken from the Section 18 assessment for propiconazole (J. R. Tomerlin, 4/14/03, DP Barcode D262299), which are 0.0005 mg/kg/day via the dermal route and 0.03 mg/kg/day via the oral route. HED notes that an assessment addressing exposure from soil has not been completed due to the conservative nature of the turf assessment and the likelihood that exposure from soil would be significantly lower than that from turf (pers. comm. J. Evans, OPP/HED, 6/16/04). Based on the propiconazole assessment and the conversion factors described above, combined direct and indirect dermal exposures are estimated to be less than 0.0001 mg/kg/day and combined oral exposures are estimated to be less than 0.0019 mg/kg/day (Table 4). The overall residential exposure is likely to be less than 0.0020 mg/kg/day. Relative to the 15 mg/kg/day point of departure, this gives an MOE of approximately 7500 for children. Based on our current set of uncertainty factors, the target MOE is 1000, indicating that the risk associated with residential exposure for children is below HED's level of concern. Adults may experience dermal exposure to parent triazole-derivative fungicide. Based on the propiconazole assessment, the adult dermal exposure estimate is slightly less than that of children. Incidental oral exposure is not expected to occur with adults.

**Table 4. Summary of Children's Residential Exposure and Risk Estimates for 1,2,4-Triazole**

| Pathway | Source | Parent Fungicide Exposure Estimate, mg/kg/day[a] | 1,2,4-Triazole Exposure Estimate, mg/kg/day[b] | MOE[c] |
|---|---|---|---|---|
| Dermal | Direct | 0.00 | 0.0000 | Not Defined |
| | Indirect | 0.0005 | 0.0001 | 150000 |
| Oral | Direct | 0.03 | 0.0012 | 13000 |
| | Indirect | 0.03 | 0.0007 | 21000 |
| Total | | | 0.0020 | 7500 |

[a] Residential exposure estimates for parent fungicides are taken from the *Propiconazole Risk Assessments for the Section 18 Request for Control of Soybean Rust*, J. R. Tomerlin, 4/14/04, DP Barcode D262299.
[b] Parent fungicide exposure estimate × metabolic conversion factor (0.17 for direct and 0.10 for indirect sources) × molecular weight conversion factor (0.24).
[c] Margin of Exposure = Point of Departure (15 mg/kg/day)/Exposure Estimate

*Drinking Water*. This assessment uses modeled estimates of 1,2,4-triazole residues in surface and ground water, as reported in the Omnibus Report, and the Drinking Water Level of Comparison (DWLOC) approach to address exposure to free triazole in drinking water. Estimated environmental concentrations (EECs) of free triazole in groundwater were obtained from the SCI-GROW model and range from 0.0 to 0.026 parts per billion (ppb), with the higher concentrations associated with uses on turf. Surface water EECs were obtained using the FIRST model. Acute surface water EECs ranged from 0.29 to 4.64 ppb for agricultural uses and up to

32.1 ppb from use on golf cours e turf. HED notes that ground water monitoring studies in New Jersey and California showed m aximum residues of 16.7 and 0.46 ppb, respectively, which exceed the SCI-GROW estimat s significantly. Contrariwise, preliminary monitoring data from USDA's Pesticide Data Prograr for 2004 show no detectable residues of 1,2,4-triazole in any drinking water samples (e-mail rom Roger Fry, USDA PDP to David Hrdy, EPA/OPP/HED dated 6/03/04), either treated or ntreated (maximum LOD = 0.73 ppb, n=40 each).

*Aggregate Exposure*. In estimating aggregate exposure, HED has combined potential dietary and non-dietary sources f 1,2,4-triazole. The dietary exposure analysis described above provides acute and chronic dieta y exposure estimates for various population subgroups. To account for the drinking water c mponent of dietary exposure, HED has used the DWLOC approach, as noted above. The DWLOC represents a maximum concentration of a chemical in drinking water at or below whic aggregate exposure will not exceed HED's level of concern. In considering non-dietary exposur , HED has used the residential exposure estimate for children and applied it to all population s ubgroups. As noted in the section on residential exposure, the non-dietary exposure estimate is considered to be highly conservative for children. Since adults are not expected to have non-die ary oral exposure to 1,2,4-triazole and that pathway makes up the majority of the residential ex posure estimate for children, application of that exposure estimate to adults is considered t o be extremely conservative. Residential exposure is expected to occur for short- and/or interm diate-term durations, and therefore is not a component in the acute or chronic aggregate expos ure assessment. In order to assess aggregate short- and intermediate-term exposure, HE has combined the residential exposure estimate and the chronic dietary exposure estimat . The chronic dietary exposure estimate serves as a background level of exposure to free triazole via food. HED notes that less than 1% of lawns in the U.S. are expected to be treated with triaz le fungicide (J. R. Tomerlin, 4/14/03, DP Barcode D262299), so the likelihood of co-occurring di tary and residential exposures is very low. The aggregation of the food and residential exposur s, and the computation of the DWLOCs is shown in Table 5.

**Table 5. Summary of Aggregate Exposure Estimates for 1,2,4-Triazole and Associated Drinking Water Levels of Comparison.**

| Population Subgroup | PAD, mg/kg/day | Exposure Estimates, mg/kg/day | | | DWLOC, µg/L[b] | EEC, µg/L |
|---|---|---|---|---|---|---|
| | | Dietary | Residential | Maximum Allowable Drinking Water[a] | | |
| **Acute** | | | | | | |
| U.S. Population | 0.015 | 0.0059 | — | 0.0091 | 320 | 32 |
| All Infants | 0.015 | 0.0115 | — | 0.0035 | 30 | 32 |
| Non-nursing infants (<1 year old) | 0.015 | 0.0127 | — | 0.0023 | 20 | 32 |
| Children 1-6 years old | 0.015 | 0.0142 | — | 0.0008 | 10 | 32 |
| Children 7-12 years old | 0.015 | 0.0063 | — | 0.0087 | 90 | 32 |
| Females 13-50 years old | 0.015 | 0.0033 | — | 0.0117 | 350 | 32 |
| Males 20+ years old | 0.015 | 0.0032 | — | 0.0118 | 410 | 32 |
| **Short/Intermediate Term** | | | | | | |
| U.S. Population | 0.015 | 0.0020 | 0.002 | 0.0110 | 390 | 32 |
| All Infants | 0.015 | 0.0039 | 0.002 | 0.0091 | 90 | 32 |
| Non-nursing infants (<1 year old) | 0.015 | 0.0048 | 0.002 | 0.0082 | 80 | 32 |
| Children 1-6 years old | 0.015 | 0.0071 | 0.002 | 0.0059 | 60 | 32 |
| Children 7-12 years old | 0.015 | 0.0034 | 0.002 | 0.0096 | 100 | 32 |
| Females 13-50 years old | 0.015 | 0.0015 | 0.002 | 0.0115 | 350 | 32 |
| Males 20+ years old | 0.015 | 0.0016 | 0.002 | 0.0114 | 400 | 32 |
| **Chronic** | | | | | | |
| U.S. Population | 0.015 | 0.0020 | — | 0.0130 | 460 | 32 |
| All Infants | 0.015 | 0.0039 | — | 0.0111 | 110 | 32 |
| Non-nursing infants (<1 year old) | 0.015 | 0.0048 | — | 0.0102 | 100 | 32 |
| Children 1-6 years old | 0.015 | 0.0071 | — | 0.0079 | 80 | 32 |
| Children 7-12 years old | 0.015 | 0.0034 | — | 0.0116 | 120 | 32 |
| Females 13-50 years old | 0.015 | 0.0015 | — | 0.0135 | 410 | 32 |
| Males 20+ years old | 0.015 | 0.0016 | — | 0.0134 | 470 | 32 |

[a] Maximum Allowable Drinking Water Exposure Estimate = PAD - (Dietary Exposure Estimate + Residential Exposure Estimate)

[b] *DWLOC = Drinking Water Level of Comparison* = Max. Allowable Drinking Water Exposure Estimate (mg/kg/day) × 1000 µg/mg × Body Weight (kg) ÷ Water Consumption (L/day). Body weight values used are 70 kg for males > 12 years of age and the U.S. population, 60 kg for females > 12 years of age, 10 kg for all groups < 13 years of age. Water consumption = 2 L/day for groups >12 years of age and the U.S. population, 1 L/day for groups < 13 years of age.

With the exception of the acute DWLOCs for infants and children 1-6, all DWLOCs are greater than the largest EEC (surface water estimate from use on turf), indicating that aggregate

exposures are not likely to exce d HED's level of concern. Although the acute DWLOCs for infants and children 1-6 indicat that aggregate exposure may exceed 0.015 mg/kg/day, HED does not believe this to be the c se due to the extremely conservative nature of the overall assessment (highest-tolerance l vel residues, 100% crop treated, 77% *in-vivo* conversion factor). Furthermore, the drinking wate monitoring data from the Pesticide Data Program found no detectable residues of either fre triazole or parent triazole-derivative fungicide in its preliminary 2004 dataset, indicating that nei her parent compounds nor 1,2,4-triazole are likely to occur in drinking water. For all exposur durations and population subgroups, HED does not expect aggregate exposure to exceed it level of concern.

*Cumulative Assessment.* The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesti ide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other th ngs, available information concerning the cumulative effects to human health that may result fr n dietary, residential, or other non-occupational exposure to other substances that have a con mon mechanism of toxicity. The reason for consideration of other substances is due to the pc sibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed o a pesticide at a level that is considered safe may in fact experience harm if that person i also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances ar also considered safe.

HED did not perform a c mulative risk assessment as part of this risk assessment for 1,2,4-triazole because HED has ot yet initiated a review to determine if there are any other chemical substances that have a nechanism of toxicity common with that of 1,2,4-triazole. For purposes of this petition, EPA h s assumed that 1,2,4-triazole does not have a common mechanism of toxicity with othe substances, including triazole-derivative fungicides that are the subject of current Section 18 em rgency exemptions and/or tolerance extensions.

On this basis, the petitio er must submit, upon EPA's request and according to a schedule determined by the Agency, such nformation as the Agency directs to be submitted in order to evaluate issues related to whethe 1,2,4-triazole shares a common mechanism of toxicity with any other substance and, if so, w ether any tolerances for 1,2,4-triazole-generating compounds need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with 1,2,4-triazole, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment.

HED has recently finaliz d its guidance for conducting cumulative risk assessments on substances that have a common m echanism of toxicity. This guidance will be available from the OPP Website (http://www.epa.go /pesticides). In the guidance, it is stated that a cumulative risk assessment of substances that ca se a common toxic effect by a common mechanism will not be conducted until an aggregate exp osure assessment of each substance has been completed.

Before undertaking a cun ulative risk assessment, HED will follow procedures for

identifying chemicals that have a common mechanism of toxicity as set forth in the *Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity* (64 FR 5795-5796, February 5, 1999).

**Conclusions**

This interim assessment is based, in all respects, on high-end assumptions regarding exposure, and the resulting exposure estimates are believed to overestimate any actual exposure to 1,2,4-triazole that may occur. Even with these assumptions, HED believes that aggregate exposure to free triazole will not exceed our level of concern. HED is planning to conduct a more sophisticated human health assessment in early 2005 following submission and review of the ongoing toxicology and residue chemistry studies for 1,2,4-triazole. That assessment will provide more realistic exposure and risk estimates, and should ease the registration review process for a number of pending triazole-derivative fungicide active ingredients.

cc: M. Doherty, J. R. Tomerlin (RD), RAB2 Reading File

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# R100946

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|---|---|
| **Chemical:** | **1H-1,2,4-Triazole (A metabolite of tebu** |
| **PC Code:** | **600074** |
| **HED File Code** | **14000 Risk Reviews** |
| **Memo Date:** | **06/29/2004** |
| **File ID:** | **DPD304288** |
| **Accession Number:** | **412-05-2000** |

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